

The association between daily step count and all-cause and cardiovascular mortality: a meta-analysis

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Aims

There is good evidence showing that inactivity and walking minimal steps/day increase the risk of cardiovascular (CV) disease and general ill-health. The optimal number of steps and their role in health is, however, still unclear. Therefore, in this meta-analysis, we aimed to evaluate the relationship between step count and all-cause mortality and CV mortality.

Methods and results

We systematically searched relevant electronic databases from inception until 12 June 2022. The main endpoints were all-cause mortality and CV mortality. An inverse-variance weighted random-effects model was used to calculate the number of steps/day and mortality. Seventeen cohort studies with a total of 226 889 participants (generally healthy or patients at CV risk) with a median follow-up 7.1 years were included in the meta-analysis. A 1000-step increment was associated with a 15% decreased risk of all-cause mortality [hazard ratio (HR) 0.85; 95% confidence interval (CI) 0.81–0.91; $P < 0.001$], while a 500-step increment was associated with a 7% decrease in CV mortality (HR 0.93; 95% CI 0.91–0.95; $P < 0.001$). Compared with the reference quartile with median steps/day 3867 (2500–6675), the Quartile 1 (Q1, median steps: 5537), Quartile 2 (Q2, median steps 7370), and Quartile 3 (Q3, median steps 11 529) were associated with lower risk for all-cause mortality (48, 55, and 67%, respectively; $P < 0.05$, for all). Similarly, compared with the lowest quartile of steps/day used as reference [median steps 2337, interquartile range 1596–4000], higher quartiles of steps/day (Q1 = 3982, Q2 = 6661, and Q3 = 10 413) were linearly associated with a reduced risk of CV mortality (16, 49, and 77%; $P < 0.05$, for all). Using a restricted cubic splines model, we observed a nonlinear dose–response association between step count and all-cause and CV mortality ($P_{\text{nonlinearity}} < 0.001$, for both) with a progressively lower risk of mortality with an increased step count.

Conclusion

This meta-analysis demonstrates a significant inverse association between daily step count and all-cause mortality and CV mortality with more the better over the cut-off point of 3867 steps/day for all-cause mortality and only 2337 steps for CV mortality.

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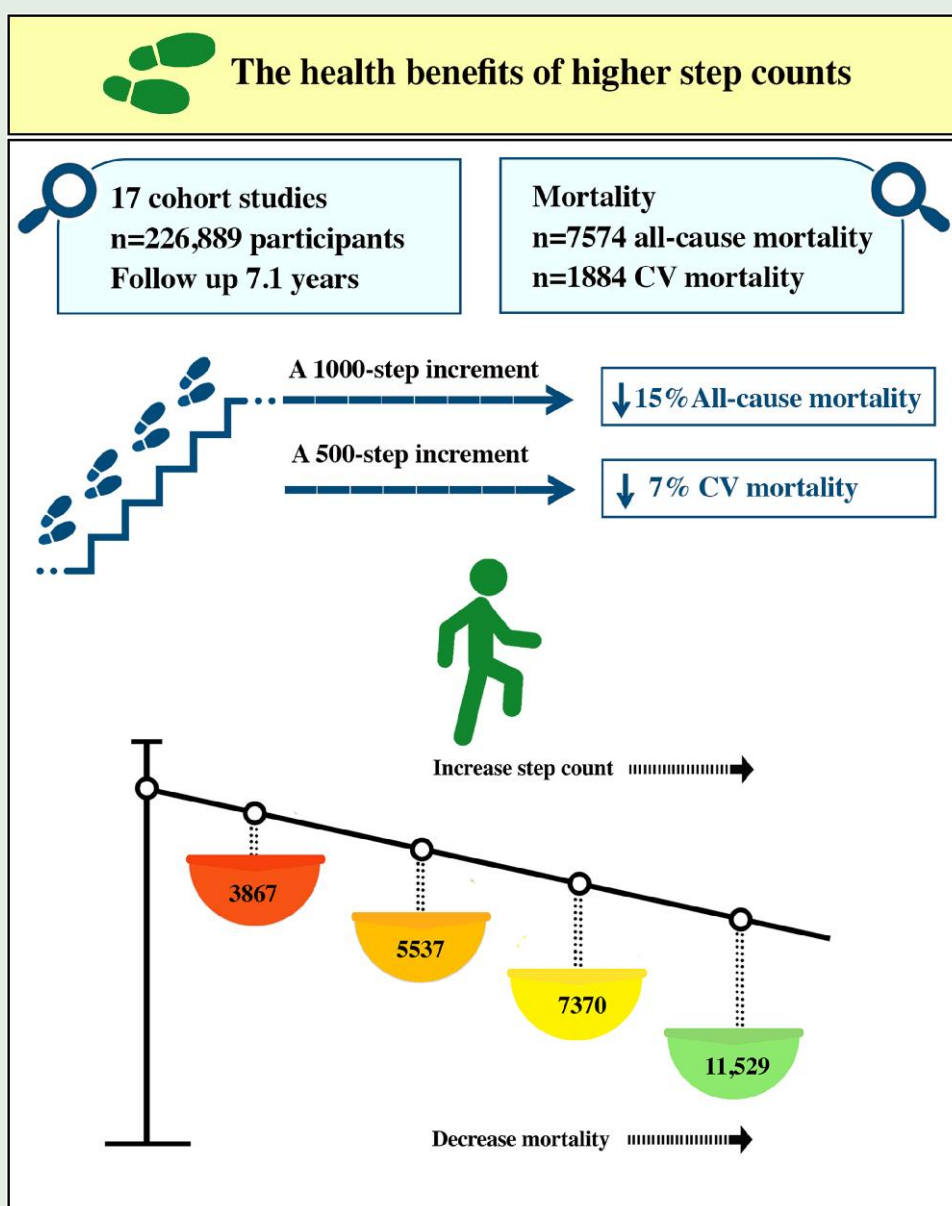
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Lay summary

- There is strong evidence showing that sedentary life may significantly increase the risk of cardiovascular (CV) disease and shorten the lifespan. However, the optimal number of steps, both the cut-off points over which we can see health benefits, and the upper limit (if any), and their role in health are still unclear.
- In this meta-analysis of 17 studies with almost 227 000 participants that assessed the health effects of physical activity expressed by walking measured in the number of steps, we showed that a 1000-step increment correlated with a significant reduction of all-cause mortality of 15%, and similarly, a 500-step increment correlated with a reduced risk of CV mortality of 7%. In addition, using the dose–response model, we observed a strong inverse nonlinear association between step count and all-cause mortality with significant differences between younger and older groups.
- It is the first analysis that not only looked at age and sex but also regional differences based on the weather zones, and for the first time, it assesses the effect of up to 20 000 steps/day on outcomes (confirming the more the better), which was missed in previous analyses. The analysis also revealed that depending on the outcomes, we do not need so many steps to have health benefits starting with even 2500/4000 steps/day, which, in fact, undermines the hitherto definition of a sedentary life.

Graphical Abstract



Keywords

Daily step counts • All-cause mortality • Cardiovascular mortality • Prevention

Introduction

Physical activity is associated with a reduction in the risk of mortality from any cause and an improvement in the quality of life.¹ In contrast, a sedentary lifestyle (usually defined as <5000 steps/day) is significantly associated with an increased risk of mortality from any cause, from cardiovascular (CV) and oncological diseases, and a greater risk of Type 2 diabetes.² Due to its high prevalence, sedentary behaviour is referred to as the disease of the 21st century.³ Epidemiological data show that insufficient levels of physical activity affect 27.5% of people worldwide, with this percentage being much higher among women than among men (23.4 vs. 31.7%) and people in high-income countries compared with low-income countries (36.8 vs. 16.2%). In recent years, it has been shown that the global prevalence of low physical activity has declined. Moreover, if current trends continue, the 2025 global physical activity target (a 10% relative reduction in insufficient physical activity) will not be met.⁴

It should be emphasized that 81% of adolescents worldwide undertake insufficient physical activity.⁵ Between 2001 and 2016, a slight reduction in the incidence of low physical activity was found among boys (77.6 vs. 80.1%), but not among girls (84.7 vs. 85.1%).⁵ According to data collated by the World Health Organization, insufficient physical activity is the fourth most frequent cause of death in the world (~1.5 billion people worldwide are physically inactive, and 3.2 million deaths a year are related to physical inactivity).^{6,7}

The COVID-19 pandemic has also resulted in reduced levels of physical activity. Before the outbreak of the COVID-19 pandemic in 2019, the worldwide average daily number of steps was 5323.⁸ The number of steps during the pandemic decreased significantly and, importantly, had not returned to baseline after 2 years.⁸ Consequently, every effort should be made to improve the global level of physical activity. Even a minimal change (from inactive to low physical activity) may bring clinically significant benefits, such as a reduction in the risk of death.⁹ The simplest form of physical activity is walking. Currently, the recommended number of steps for most people by the Centers for Disease Control and Prevention (CDC) is 10 000 steps/day. As already mentioned, the average daily number of steps before the COVID-19 pandemic was 5323 (USA: 4774; UK: 5444; China: 6189), which is substantially less than the CDC recommendation.¹⁰ It is worth emphasizing that what really matters is the number of daily steps taken, not necessarily the intensity of exercise. In a study of 4840 Americans, it was found that a greater number of daily steps was significantly associated with lower all-cause mortality; however, no significant association between step intensity and mortality was seen after adjusting for the total number of steps/day.¹¹

Despite these emerging benefits of walking for public health, current European guidelines for physical activity have not yet released specific recommendation on the optimal number of steps/day needed for good health and longevity.^{12,13} Any approach to increase the population level of physical activity through the promotion of safe, accessible, and environmentally friendly activities is insufficient without a recommendation for a defined level of physical activity. The widespread availability of step counters (smart watches, cell phones, and pedometers) means that they are increasingly used to self-monitor physical activity. Moreover, the use of pedometers can contribute to an increase in the number of steps taken per day. In a meta-analysis of 70 randomized clinical trials, it was shown that step-count monitoring leads to short- and long-term increases in step count.¹⁴

Based on the above, the aim of this meta-analysis was to evaluate the dose–response relationship between step count and all-cause and CV mortality.

Methods

Search strategy and selection criteria

We followed the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.¹⁵ Due to the study design (meta-analysis),

neither Institutional Review Board approval nor patient informed consent was required.

The Population, Exposure, Comparator, Outcomes, Study (PECOS) characteristic model was used to shape the clinical question and to build the search strategy (see [Supplementary material online, Table S1](#)). The following databases were searched from inception to 12 June 2022: PubMed-Medline, Scopus, EMBASE, Web of Science, Google Scholar, the Cochrane Central Registry of Controlled Trials, and ClinicalTrials.gov. Search terms were related to daily number of steps and mortality using the following key words: daily steps, step count, physical activity, physical exercise, low physical activity, moderate physical activity, vigorous physical activity, clinical outcomes, mortality, all-cause mortality, CV mortality, and adults (see [Supplementary material online, Table S2](#)). Additional searches for potential studies included the references of review articles and the abstracts from the subject congresses such as scientific sessions of the European Society of Cardiology (ESC), ESC Preventive Cardiology, European Atherosclerosis Society, the American Heart Association, and American College of Cardiology. The wild-card term '*' was used to enhance the sensitivity of the search strategy. The literature search was limited to articles published in English and to human studies. No filters were applied. Two reviewers (S.S. and J.L.) independently and separately evaluated each article. Disagreements were resolved by discussion with the senior investigators (I.B. and M.B.). The remaining articles were obtained in full text and assessed by the same two researchers. For each article, the risk of bias was independently assessed by the same investigators using the assessment of risk of bias in cohort studies, the Newcastle–Ottawa Scale (NOS). Three domains were evaluated with the following items: (i) selection, (ii) comparability, and (iii) exposure. The risk of bias in each study was judged to be 'good', 'fair' or 'poor'.¹⁶

Articles were considered eligible if they reported the role of daily number of steps in the general population: (i) longitudinal studies investigating daily number of steps and relationship with all-cause mortality and/or CV mortality, (ii) enrolled population of adults aged ≥18 years, and (iii) articles in English. Exclusion criteria were: (i) if participants were not recruited from a general healthy population (healthy subjects and/or individuals with CV risk factors; [Supplementary material online, Table S3](#)) and (ii) if articles reported the association with other exposures and diseases. If the study populations had been reported more than once, the results of studies with a more extended follow-up period were used.

Outcome variables

The daily number of step counts in the included studies was objectively measured for at least seven consecutive days using validated methods with the application of pedometers (e.g. DIGI-WALKER DW-200) and/or accelerometers (e.g. Axivity AX3, ActiTrainer, ActiGraph 7164, GT1M, and wGT3X-BT).

The main endpoints were all-cause mortality and CV mortality and their relationship with different quartiles of steps as well as the dose–response relationship. The secondary endpoints were related to the impact of age ranges, sex, and geographical regions (based on available data from the climate regions) on step count and dose–response relationship with the main investigated outcomes.

Data synthesis and statistical analysis

The meta-analysis was conducted using R Statistical Software (v3.5.1, Boston, MA, USA), using the packages 'dosresmeta' and the RevMan [Review Manager (RevMan) Version 5.1, The Cochrane Collaboration, Copenhagen, Denmark]. The hazard ratio (HR) and 95% confidence interval (CI) were estimated as the effect size for all studies, and relative risk (RR) was considered equivalent to HRs, while an odds ratio was converted to HR using the formula by Zhang and Yu.¹⁷ We conducted a meta-analysis of effect estimates using an inverse-variance weighted random-effects models, calculating pooled HRs and 95% CIs. We used a cut-off of HR for an increment of 1000 steps/day for all-cause mortality and 500 steps/day for each study on CV mortality. Likewise, we calculated the median [interquartile range (IQR)] steps/day by quartile for total sample, extracting it from each individual study. The quartile with the lowest number of daily steps was considered as the reference quartile, and the risk difference and 95% CI were calculated in comparison with reference line.

Table 1 Main characteristics of the trials included in the present meta-analysis

Study year	Location	Study entry	Steps measurements	Monitoring period	Steps/day	Sample size (N/C)	Endpoints	Follow-up (years)
Dwyer 2015 ²²	Australia	2000	Omron HJ-003/102 Omron Healthcare Yamax Digi-Walker SW-200	2 days	≤5550 5551–8000 8001–10 000 10 001–13 500 >13 500	2576/219	All-cause mortality	10
Fox 2015 ²³	UK	2007–08	ActiGraph GT1Ms	7 days	<3196 3196–5170 >5170	213/33	All-cause mortality	4.5
Cochrane 2017 ²⁴	USA	2010–13	ActiGraph GT3x	7 days	2681 ± 1475 (per 500)	1590/234	CV mortality	2.7
Yamamoto 2018 ²⁵	Japan	1998–99	EC-100S	7 days	<4503 4503–6110 6111–7971 >7971	419/76	All-cause mortality	9.8
German 2019 ²⁶	USA	2005–06	ActiGraph AM-7164	7 days	<2500 2500–4999 5000–7500 7500–9999 >10 000	4055/474/ 108	All-cause mortality CV mortality	12
Jefferis 2019 ²⁷	UK	2010–12	ActiGraph GT3x	7 days	<2927 2928–4532 4533–6412 6412–17 781	1181/194	All-cause mortality	5.0
Lee 2019 ²⁸	USA	2011–12	ActiGraph GT3x+	7 days	2128–3202 3992–4738 5493–6403 7580–9954	16 741/504	All-cause mortality	4.3
Jefferis 2019 ²⁹	UK	2010–12	ActiGraph GT3x	7 days	<2943 2944–4540 4541–6406 6407–17 781	1274/122	CV mortality	4.9
Oftedal 2020 ³⁰	Australia	2005–08	ActiGraph 7164 Pansacola	7 days	4689–8850 Per 1000-step increment	1697/204	All-cause mortality	9.6
Hansen 2020 ³¹	Norway	2008–09	ActiGraph GT1M Pansacola	7 days	2495–5325 6388–7350 8215–9186 10 556–13 110	2183/119	All-cause mortality	9.1
Saint-Maurice 2020 ¹¹	USA	2003–06	ActiGraph 7164 Pansacola	7 days	4000 8000 12 000	4840/1165 /406	All-cause mortality CV mortality	10.1
LaCroix 2020 ³²	UK	2012–14	ActiGraph GT3x	7 days	Per 1000-step increment	6389/175	CV mortality	5.0
Moniruzzaman 2020 ³³	Japan	2006–08	ActiGraph GT3x	7 days	<6060 6061–8174 8175–10 614 >10 615	6379/175	CV mortality	5.0
Mañas 2022 ³⁴	Spain	2015–17	ActiGraph 7164 Pansacola	7 days	5835 ± 3445 Per 1000 steps	768/45	All-cause mortality	5.7

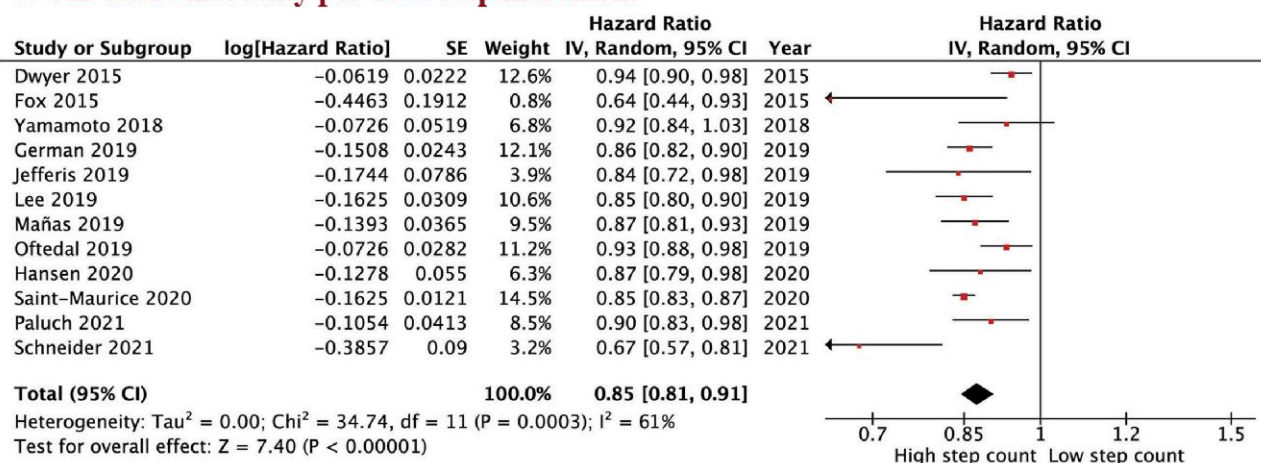
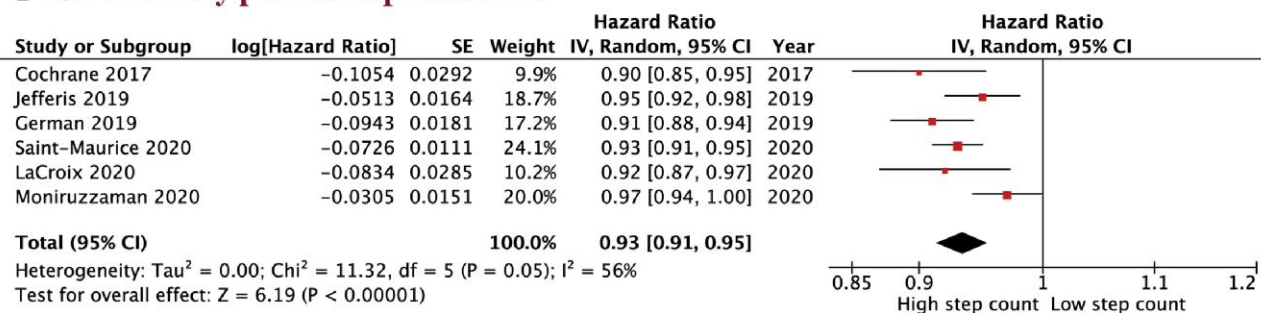
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Table 1 Continued

Study year	Location	Study entry	Steps measurements	Monitoring period	Steps/day	Sample size (N/C)	Endpoints	Follow-up (years)
Paluch 2021 ³⁵	USA	2005–06	ActiGraph 7164	7 days	<7000 7000–10 000 >10 000	2110/72	All-cause mortality	10.8
Schneider 2021 ³⁶	UK	2013–15	Axivity AX3	7 days	6500 8000 9250 12 000	95 974/2290	All-cause mortality	5.5
Del Pozo Cruz 2022 ³⁷	UK	2013–15	Axivity AX3	7 days	1539–5385 5385–8821 >8821	78 500/ 2179/664	All-cause mortality CV mortality	7

CV mortality cases = 937, 2075, 1601.

CV, cardiovascular; N, numbers; C, cases.

A All-cause mortality per 1000 step increment**B CV mortality per 500 step increment****Figure 1** The relationship between step increment and outcome: (A) all-cause mortality per 1000-step increment; (B) cardiovascular mortality per 500-step increment.

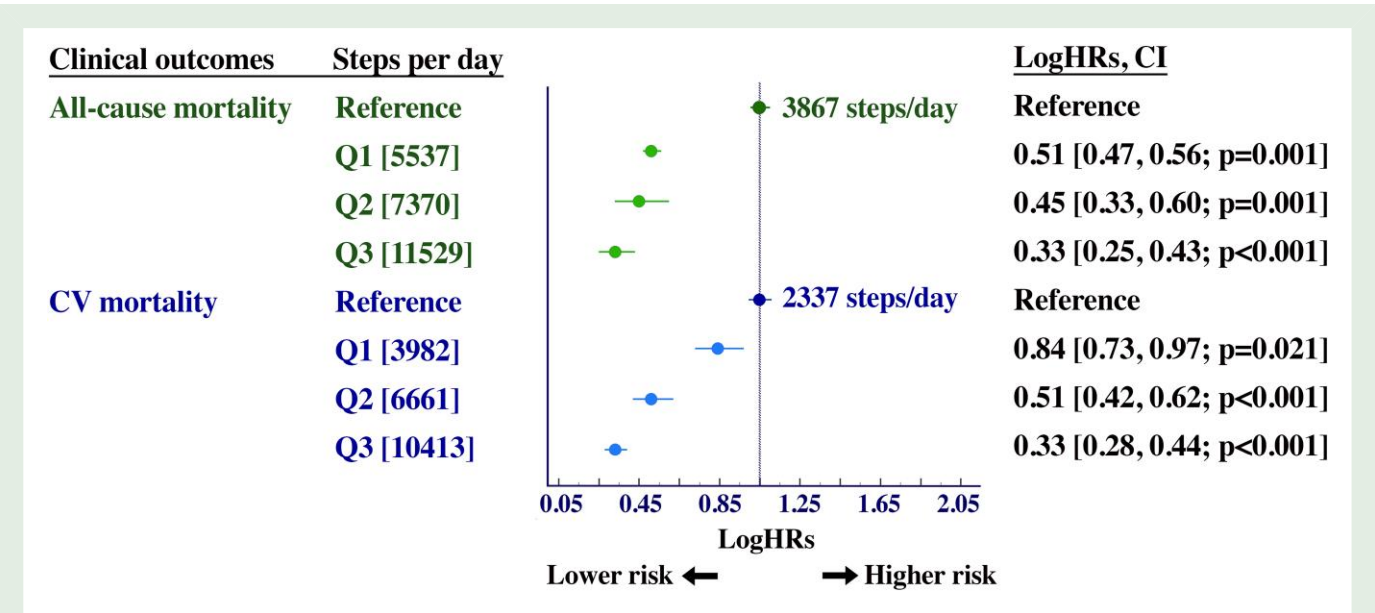


Figure 2 The relationship between number of steps/day in different quartiles and outcomes.

In addition, we performed the dose–response analysis by generating restricted cubic spline models using three or more quantitative categories (25th, 50th, and 75th percentiles) to examine the potential dose–response relationship between steps and mortality.^{18,19} The Wald test was used for linearity or nonlinearity to test the null hypothesis that the coefficient of the spline transformation was equal to zero.²⁰ Heterogeneity between studies was assessed using the Cochrane Q test and I² index. As a guide, I² < 25% indicated low, 25–50% moderate, and >50% high heterogeneity.²¹ P-values of <0.05 were considered statistically significant. Publication bias was assessed using visual inspections of funnel plots and Egger’s test.

Results

Study selection and patient population

A total of 5301 articles were identified from the search after discarding duplicates from the different databases. These articles were first screened by title and abstract, leading to 65 potential articles that underwent a full-text review. After a stringent selection process, a total of 17 cohort studies with 226 889 individuals and a median follow-up of 7.1 years were included in the analysis (see [Supplementary material online, Figure S1](#)).^{21–37} Out of 17 studies, 10 studies reported all-cause mortality,^{22,23,25,27,28,31,32,34–36} 4 studies reported CV mortality,^{24,29,32,33} and 3 studies reported both outcomes.^{11,26,37} The characteristics of the included studies are presented in [Table 1](#).

The mean age of participants was 64.4 ± 6.7, and 48.9% were females. The frequency of alcohol users was higher compared with current smokers (49.9 vs. 20.7%; P = 0.01). The education of participants with more than high school was 55.4%. The other cardiac risk factors are presented in the [Supplementary material online, Table S3](#).

Daily step counts with all-cause and cardiovascular mortality

A 1000-step increment was associated with a 15% decreased risk of all-cause mortality (HR 0.85; 95% CI 0.81–0.91, P < 0.001), while a 500-step increment was associated with 7% decrease of CV mortality (HR 0.93; 95% CI 0.91–0.95, P < 0.001; [Figure 1A and B](#)). Compared with the reference quartile with median steps/day 3867 (IQR 2500–

6675), the Quartile 1 (Q1, median steps: 5537), Quartile 2 (Q2, median steps 7370), and Quartile 3 (Q3, median steps 11 529) were associated with lower risk of all-cause mortality (by 48, 55, and 67%, respectively; P < 0.05, for all). Similarly, compared with the lowest quartile of steps/day (median steps 2337, IQR 1596–4000) higher quartiles of steps/day (Q1 = 3982, Q2 = 6661, and Q3 = 10 413) were associated with a reduced risk of CV mortality (by 16, 49, and 77%, respectively; P < 0.05, for all; [Figure 2](#)).

Using a restricted cubic splines model, we observed a strong inverse dose–response association between step count and all-cause death (P_{nonlinearity} < 0.001; [Figure 3A](#)). According to the spline model, a significant association was also reported between step count and CV mortality (P_{nonlinearity} < 0.001; [Figure 3B](#)). The shape of the spline model dose–response curve was similar for males and females without significant differences in all-cause mortality and CV mortality (P = 0.21; [Figure 4A and B](#)). In contrast, the RRs in older adults (≥60 years) were lower compared with younger participants (<60 years; P = 0.009) with lower step-count levels at the phase of the curve with the most pronounced mortality reduction: in the older age group (≥60 years), the sharpest phase of the curve was at ~6000–10 000 steps (0.38/0.09 = 42.3% risk reduction), while for the younger age group (<60 years), this sharpest phase was at 7000–13 000 steps (0.39/0.08 = 48.7% risk reduction). According to the spline model, a daily steps higher than 5000 results in a dramatically lowering risk of all-cause mortality ([Figure 5A and B](#)). In addition, the analysis comparing the impact of climate regions on the relationship between step count and all-cause mortality showed no statistically significant effect on all-cause mortality. When the steps exceeded ~5500 steps/day, the RRs of all-cause mortality decreased sharply in people in all climate zones (temperate, subtropical, subpolar, and mixed zone) without significant differences between the groups (see [Supplementary material online, Figure S2](#)).

Risk of bias assessment

The assessment of the risk of bias in the included studies using NOS for cohort studies showed that most studies had moderate-to-high quality in defining objectives and the main outcomes (see [Supplementary material online, Tables S4](#)).

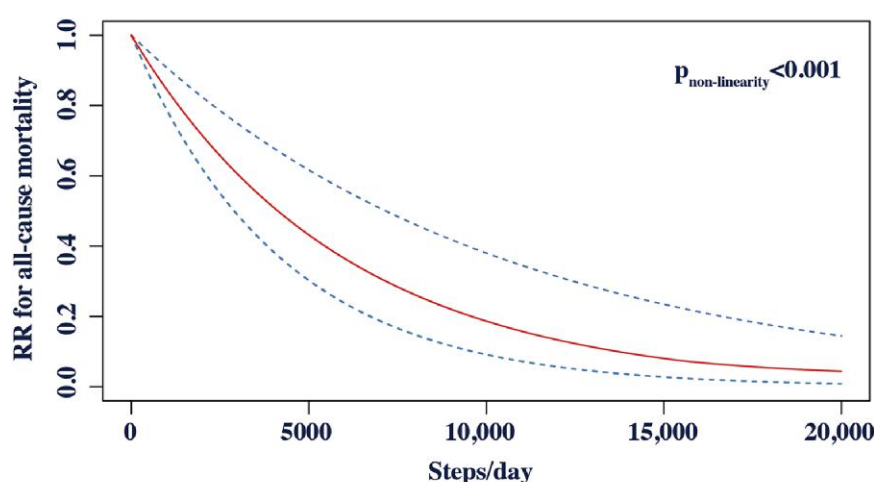
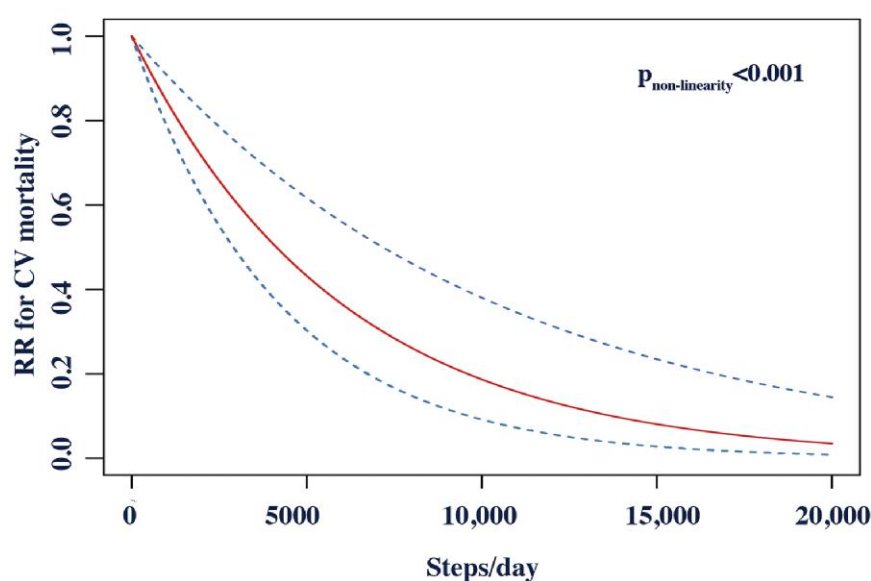
A Association between steps per day and risk for all-cause mortality**B Association between steps per day and risk for CV mortality**

Figure 3 Nonlinear dose–response analyses of step count and outcome: (A) all-cause mortality; (B) cardiovascular mortality.

Discussion

In this meta-analysis of 17 studies that assessed the health effects of physical activity expressed by walking measured in number of steps, we showed that a 1000-step increment correlated with a reduction of all-cause mortality of 15%, and similarly, a 500-step increment correlated with a reduced risk of CV mortality by 7%. In addition, using the dose–response model, we observed a strong inverse nonlinear association between step count and all-cause mortality with significant differences between younger and older groups. No significant impact of sex and climate on outcomes was observed. To the best of our knowledge, this is the biggest meta-analysis published so far with additional analyses that may give new insights into the impact of regular physical activity on health and longevity.

Over the last decade, several studies have evaluated the association between step counts and clinical events (all-cause mortality and CV mortality).^{21–37} Previous meta-analyses of different cohorts showed the benefits of increased daily steps on clinical outcome, but they did not investigate the impact of demographic and climate variables on the relationship between step count and clinical events. Furthermore, analyses were limited to step counts of ~13 000.^{38–40} Recently, data from another meta-analysis included 15 studies, of which 8 were unpublished (these data are still not available). This study only addressed all-cause mortality, and the total sample size was <50 000 participants.⁴¹

In a meta-analysis by Sheng *et al.*³⁸ (16 studies with 147 344 participants), the reduction of all-cause mortality and CV diseases was similar to our findings: a 1000 steps increment was associated with 13% risk

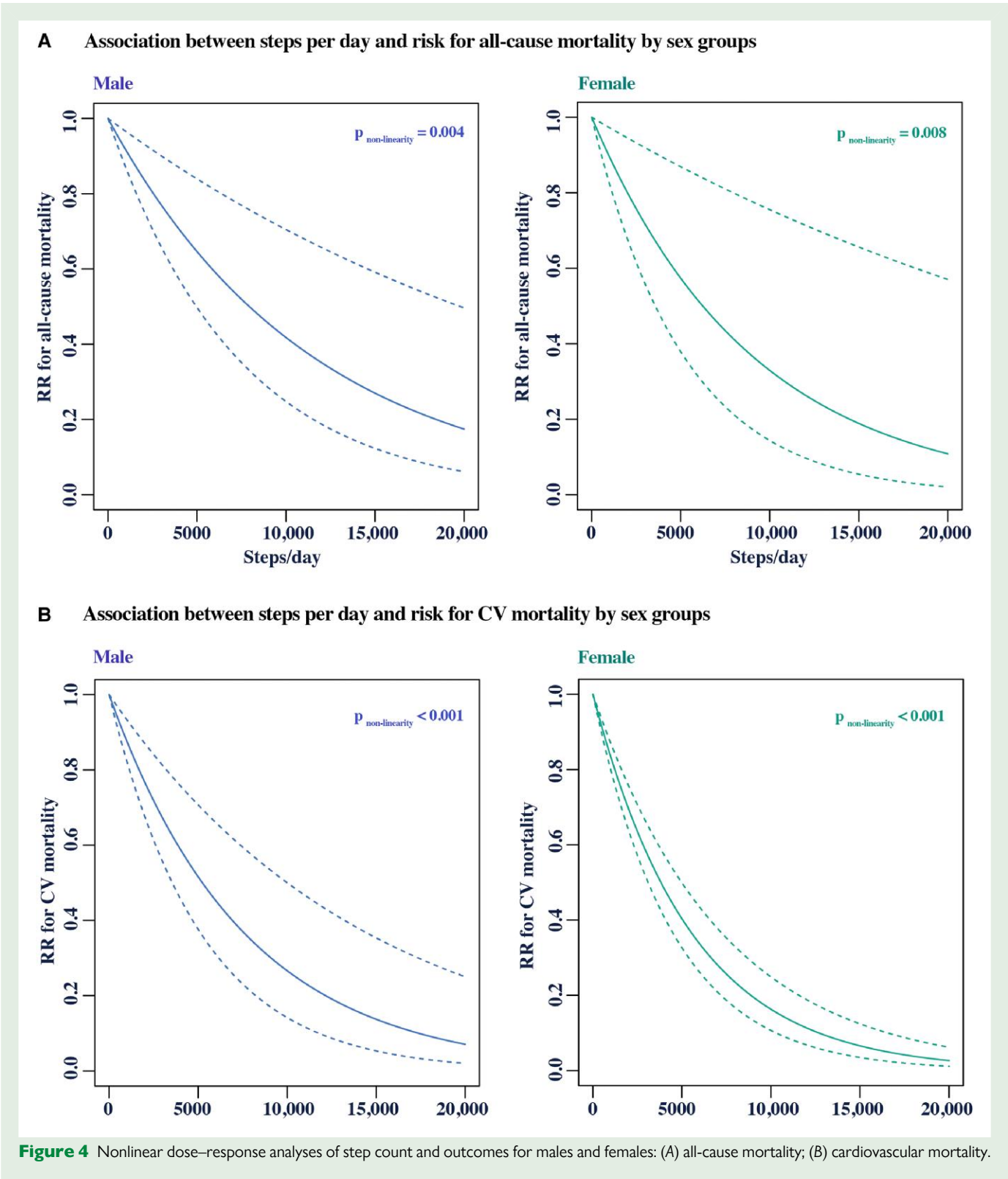
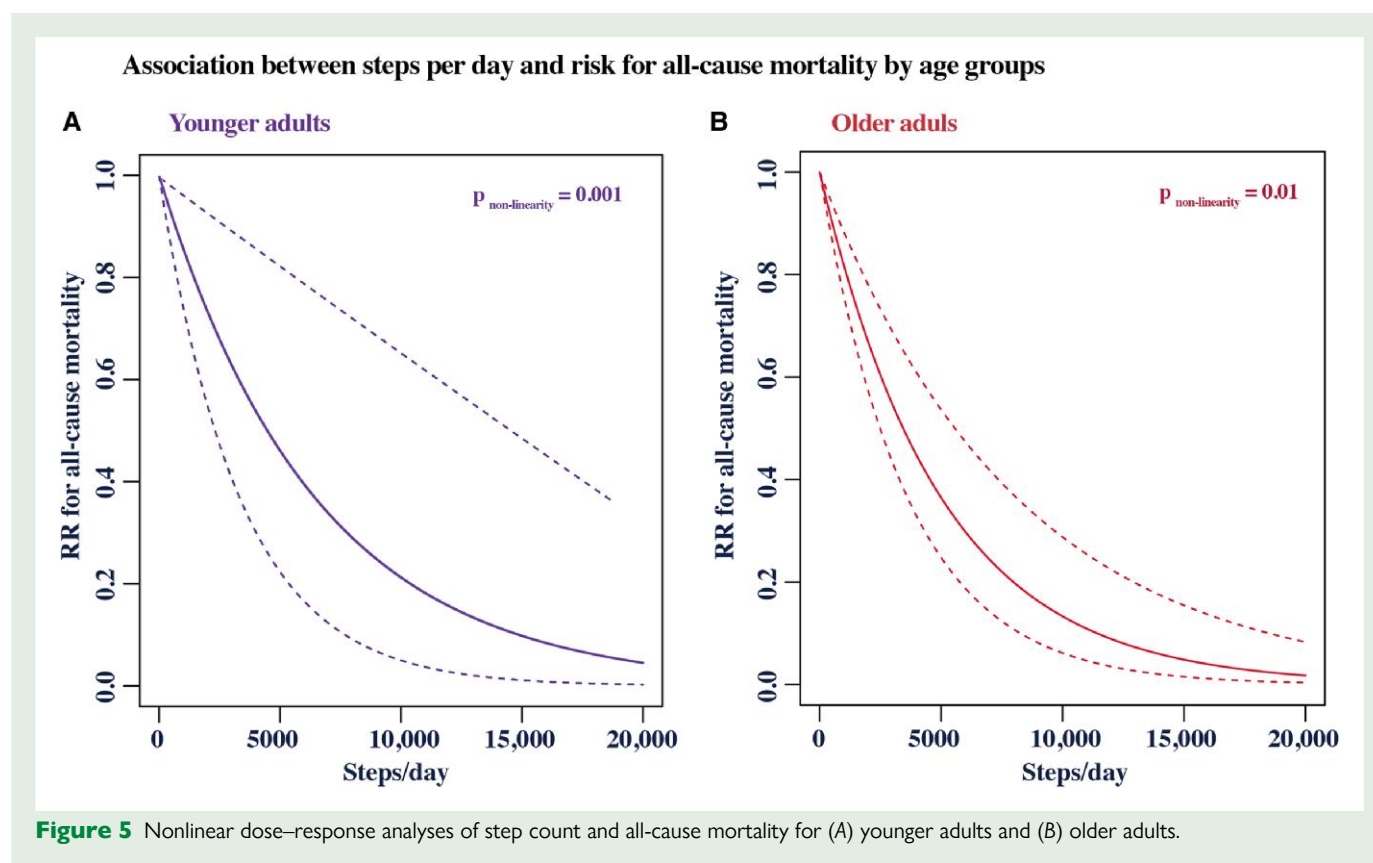


Figure 4 Nonlinear dose–response analyses of step count and outcomes for males and females: (A) all-cause mortality; (B) cardiovascular mortality.

reduction (RR 0.87; 95% CI 0.84–0.91), and for each additional 500 steps, reduction of the risk of CV diseases (and not CV mortality as in our study) was 6% (RR 0.94; 95% CI 0.91–0.97). Another meta-analysis assessed 15 studies (among which again 8 were unpublished) with papers published up to 2018.³⁹ The authors showed that

for each 1000 daily step-count increase at baseline, risk reductions in all-cause mortality were 6–36% and for cardiovascular disease (CVD), 5–21% at follow-up. There was no evidence of any significant interaction by age, sex, health conditions, or behaviours (e.g. alcohol use, smoking status, and diet) among studies that were tested for



interactions.³⁹ However, in all previous studies, the number of steps/day was up to 15 000 steps; thus, our study was the first to evaluate the health benefits with a step count of up to 20 000 steps. Moreover, in contrast to the above-mentioned study by Hall *et al.*,³⁹ we did not see any diminishing effect or risk plateau for any of the investigated groups, despite significant differences between age (<65 and ≥65). It needs to be emphasized, however, that the data with the step counts up to 20 000 steps/day are still very limited, and these results need to be confirmed in larger cohorts.

All available studies on steps number focus on increasing steps/day; however, the optimal amount of daily step count has not yet been determined. Current ESC guidelines, besides highlighting the predominance of a sedentary lifestyle in the population, confirm the benefits of any level of physical activity.⁴² What is more important, the guidelines do not offer any specific amount of physical activity (with reference to the required time duration of the exercises per day or week), which should be achieved, explaining that the data are still inconsistent and controversial.^{42–44} At the same time, the role of physical activity is equated with pharmacotherapy. Therefore, our analysis demonstrates that ‘more is better’ with respect to step counts in both sexes—irrespective of age and the location where walking takes place. In addition, the results indicate that as little as 4000 steps/day are needed to significantly reduce all-cause mortality, and even fewer steps are required for a significant reduction in CV death.

Strength and limitations

The strengths of our meta-analysis include the substantial statistical power, resulting from the large sample size and the approach to statistical analysis. Moreover, the methodology of monitoring steps was similar in >94% of the included studies. In contrast to previously published meta-analyses on this topic, our study included only data from

published papers, which makes the results more reliable and verifiable. The combined data from numerous studies determines clinically significant benefits of walking, and unlike previous studies, the step count was not limited between 10 000 and 16 000 steps/day. Another strength is the prospective design of the included studies and the fact that steps were measured using external devices, thereby eliminating the risk of the bias associated with self-reporting. Moreover, most of the included studies were of high quality. We also confirmed, for the first time, that the associations between step counts and all-cause mortality are comparable in different places of the world. Our results may help to re-define both the definition of activity levels (especially sedentary, which was hitherto defined as the number of steps <5000/day) and the recommendations on the required number of steps required to achieve significant health benefits.⁴⁵

This study has some limitations. One of them is the observational character of the included studies. The impact of count steps was also not tested in different disease states; however, in this analysis, we wanted to focus mainly on the primary preventive role of step counts. The methods of calculation of step count were not identical in all included studies. To address this heterogeneity, we applied the inverse-variance weighted random-effects model to calculate the number of steps/day and clinical outcomes. We were unable to investigate the impact of race and different socioeconomic status as well as data concerning lifestyle. We cannot also exclude the possibility of reverse causality of observed results, and the effect of other coexisting risk factors on the investigated outcomes (e.g. whether sedentary life or comorbidities influenced the final results, or whether those more active were also healthier), even though we excluded the participants not recruited from a general healthy population and from the studies that reported the association with other exposures and diseases as well as we selected models adjusted for demographic and clinical indices in our analysis; future studies may be required to test the impact of coexistence of

regular exercise with different comorbidities on survival in the general population. Additionally, the number of studies with over 20 000 steps/day is very limited, and further studies are required to expand the pool of data in this area.

Conclusions

In this meta-analysis of 17 studies, a statistically significant inverse association between the daily step count and all-cause mortality and CV mortality was observed. Our results may be used to promote public awareness of the importance of physical activity, particularly in the easily implementable activity of walking.

Authors' contribution

M.B. and I.B. contributed to the conception and design of the work; M.B., I.B., J.L., and S.S. contributed to the acquisition and interpretation of data; M.B., J.L., S.S., and P.E.P. drafted the manuscript; M.B. and I.B. contributed to the analysis and interpretation of data; M.B., I.B., J.L., S.S., P.E.P., Z.R., S.S.M., A.S., A.B.D., M.Y.H., and G.B. critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Data availability

The data underlying this article will be shared on reasonable request with the corresponding author.

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